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Tyrosinase-related protein 1 mRNA expression in lymph node metastases predicts overall survival in high-risk melanoma patients

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Research Report

Physical Exercise for Patients Undergoing Hematopoietic Stem Cell Transplantation: Systematic Review and Meta-Analyses of Randomized Controlled Trials

Inge E.P.M. van Haren, Hans Timmerman, Carin M. Potting, Nicole M.A. Blijlevens, J. Bart Staal, Maria W.G. Nijhuis-van der Sanden

Background. The treatment-related burden for patients undergoing hematopoietic stem cell transplantation (HSCT) may be relieved by physical exercises.

Purpose. The purpose of this study was to summarize and analyze the evidence provided by randomized controlled trials (RCTs) on physical exercise interventions among patients with cancer undergoing HSCT.

Data Sources. PubMed, CINAHL, EMBASE, the Cochrane Library, and PEDro were searched for relevant RCTs up to October 1, 2011.

Study Selection. Two reviewers screened articles on inclusion criteria and indentified relevant RCTs.

Data Extraction. Two authors assessed the selected articles for risk of bias. Data extraction was performed by 1 reviewer. Meta-analyses were undertaken to estimate the outcomes quality of life (QOL), psychological well-being and distress, and fatigue.

Data Synthesis. Eleven studies were included, with study populations consisting of recipients undergoing either an allogeneic or autologous HSCT (n=734). Four studies had low risk of bias. The exercise interventions were performed before, during, and after hospitalization for the HSCT. Different exercise programs on endurance, resistance and/or activities of daily living training, progressive relaxation, and stretching were used. Meta-analyses showed that exercise during hospitalization led to a higher QOL (weighted mean difference=8.72, 95% confidence interval=3.13, 14.31) and less fatigue (standardized mean difference=0.53, 95% confidence interval=0.16, 0.91) in patients with an allogeneic HSCT at the moment of discharge from the hospital. No marked effects were found for psychological well-being and distress. Individual study results suggested significant positive effects on QOL, fatigue, psychological well-being and distress, and physical functioning.

Limitations. Prevalent shortcomings in the included studies were the heterogeneity among studies and the lack of blinding of participants, personnel, and outcome assessment.

Conclusions. The results suggest that recipients of HSCT may benefit from physical exercise.

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Cancer is a leading cause of death worldwide, accounting for an estimated 7.6 million deaths (about 13% of all deaths) in 2008.[1] Greater understanding of the disease processes and the development of more effective therapies has resulted in a gradual increase in survival rates of patients with cancer.[2,3] The most effective treatments for hematological malignancies involve high-dose chemotherapy and, if appropriate, total-body irradiation followed by hematopoietic stem cell transplantation (HSCT). The use of HSCT continues to increase as treatment technology improves, which has resulted in reduced morbidity and an increased life expectancy.[4] Worldwide, about 50,000 people receive an allogeneic or autologous HSCT each year, with a concomitant rise in the number of survivors.[4] Despite these promising improvements, the treatment-related burden of HSCT is still high, with 2 of every 5 patients given allogeneic HSCT for advanced cancer dying from the complications.[4] Patients experience considerable physical and functional deterioration and diminished psychological well-being before, during, and after HSCT.[5]

Courneya and Friedenreich[6,7] previously described the treatment-related psychophysical problems of patients with cancer in 1999. Currently, the most relevant and frequently reported problems for patients with hematological malignancies are reduced physical performance and fitness, fatigue, psychological problems such as distress and fear, immunologic and hematologic changes, and complications such as graft versus host disease (GVHD), infections, diarrhea, and pain.[5] Severe fatigue is considered to be a significant impairment.[8] Prevalence estimates of fatigue during treatment for cancer range from 25% to 75%.[9] After transplantation, the individual's quality of life (QOL), social role, and physical function often are adversely influenced by difficulties in reintegrating into the community.[5,10] After treatment, patients generally increase the amount of physical exercise, but not to the pretreatment level. Consequently, muscular weakness and cardiorespiratory dysfunction may develop.[11] To avoid cancer-related fatigue, patients are traditionally advised to rest, minimize strenuous physical effort, and lower their daily activity in order to avoid discomfort.[8,12] However, these recommendations may have paradoxical effects because inactivity will not return the patient to his or her previous level of functioning.[13]

Over the last few years, the number of reports on the promising role of physical exercise programs as a nonpharmacologic adjuvant therapy for patients with cancer has been increased. These patients may benefit in terms of improved fitness levels, physical activity, and QOL while combating the treatment-related symptoms. In 1986, the first study to examine the effects of exercise among patients with acute leukemia already showed the positive effects of rehabilitation measures taken after HSCT.[14] Currently, various exercise interventions can be implemented before, during, and after cancer treatment, although a firmer evidence base in support of these programs is still needed.[2,5,15,16]

The purpose of this review is to systematically summarize and analyze the effects of exercise interventions administered before, during, and after HSCT on QOL, psychological well-being and distress, fatigue, and physical functioning. This overview will emphasize the exercise program and its potential physical and psychosocial benefits.

Method

This systematic review was carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) Statement.[17]

Data Sources and Searches

A comprehensive literature study was conducted using the electronic online literature databases PubMed, CINAHL, EMBASE, the Cochrane Library, and PEDro to identify relevant randomized controlled trials (RCTs).

Study Selection

Randomized controlled trials were considered eligible if they met the following inclusion criteria: (1) original article published before October 1, 2011; (2) involving patients aged 18 years or older diagnosed with cancer and undergoing HSCT; (3) physical exercise being the main component of the intervention; and (4) published in English. The following key words were used to identify relevant studies: "Stem cell," "Stem cell transplantation," "Bone marrow transplantation," "Hematologic stem cell transplantation," "Exercise," "Exercise program," "Exercise testing," "Physical activity," "Physical therapy," "Physiotherapy," "Training," "Functionality" (MESH terms or

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- eFigure 1: Forest Plot of Weighted Mean Difference, With 95% Confidence Interval, for Psychological Well-Being and Distress (Anxiety) Measured With the Hospital Anxiety and Depression Scale at Discharge From the Hospital
- eFigure 2: Forest Plot of Weighted Mean Difference, With 95% Confidence Interval, for Psychological Well-Being and Distress (Depression) Measured With the Hospital Anxiety and Depression Scale at Discharge From the Hospital

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Table 1.
Quality Assessment (Method: Cochrane Collaboration's Tool for Assessing Risk of Bias)

	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Total
Article	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Anything Else, Ideally Prespecified	Low on Risk of Bias
Hacker et al, 2011[31]	High	High	High	High	High	Low	High	1/7
Wiskemann et al, 2011[32]	Low	High	High	High	Low	Low	Low	4/7
Knols et al, 2010[33]	Low	Low	High	Low	Low	Low	Low	6/7
Baumann and colleagues, 2010/2011[25,26,a]	Low	Unclear	High	High	Low	Low	Low	5/7
Shelton et al, 2009[27]	High	High	High	High	High	Low	Low	2/7
Jarden and colleagues, 2009/2009[23,24,a]	Low	High	High	High	Low	Low	Low	4/7
Coleman et al, 2008[29]	High	High	High	High	Low	Low	Low	3/7
DeFor et al, 2007[30]	High	High	High	Low	High	Low	Low	3/7
Kim and Kim, 2005/2006[21,22,a]	Low	High	High	High	High	Unclear	Low	2/7
Coleman et al, 2003[28]	High	Low	High	High	High	Low	High	2/7
Mello et al, 2003[34]	High	High	High	High	High	Unclear	High	0/7

[a] Both publications represent 1 study.

free-text words), and "Randomized Clinical Trial." The full search strategy for CINAHL was: (MH "Hematopoietic Stem Cells") OR (MH "Stem Cells+") OR (MH "Hematopoietic Stem Cell Transplantation") OR (MH "Colony-Forming Units Assay") OR "Stem Cell" AND "Exercise." The unique articles were checked for relevance. From the selected articles, the abstracts were read to identify relevant information. In case of uncertainty, the full article was read by 2 independent reviewers (H.T. and J.B.S.). The selected articles then were read in full to confirm eligibility. Additional studies were located by a manual search using references from the retrieved articles.

Data Extraction and Quality Assessment

The Cochrane Collaboration's tool for assessing risk of bias was used to assess the risk of bias.[18] Nine items were scored, and these items were divided into 6 domains of bias (Tab. 1),[18] with 3 rating categories available for each item: (1) low risk of bias, which is unlikely to alter the results significantly; (2) unclear risk of bias, which raises some doubt about the results; and (3) high risk of bias, which seriously weakens confidence in the results. When there was insufficient information on an item or domain, it was scored as "high risk." All selected articles were scored by 2 authors (H.T. and J.B.S.). Disagreement between the assessors was resolved by discussion, and in case of remaining discussion, a third assessor (I.vH.) was asked for advice in order to make a final decision.

Data extraction was performed by one reviewer (I.vH.) using a standardized extraction form and controlled by the first rater (H.T.). In case of obscurity (to avoid potential errors), correctness of abstraction and interpretation were discussed with the first rater.

Data Synthesis and Analysis

Treatment effects were examined through meta-analyses, which were conducted only if studies were thought to be clinically homogenous and comparable in intervention, duration, and follow-up moments. The findings of the individual studies were analyzed in meta-analyses using Review Manager (RevMan) software.[19] Our main outcomes were QOL, psychological well-being and distress, fatigue, and physical functioning. Weighted mean differences (WMDs) and 95% confidence intervals (95% CIs) were calculated for each of the continuous outcome variables when equal outcome measures were used across studies. Standardized mean differences (SMDs) were used as a summary statistic when different outcome measures were used across studies to measure the same construct. A P value of $\leq$.05 was considered statistically significant.

Heterogeneity of treatment effects among studies was investigated statistically using the heterogeneity I^2 statistic. The degree of heterogeneity was graded as low (I^2<25%), moderate (I^2=25%–75%), or high

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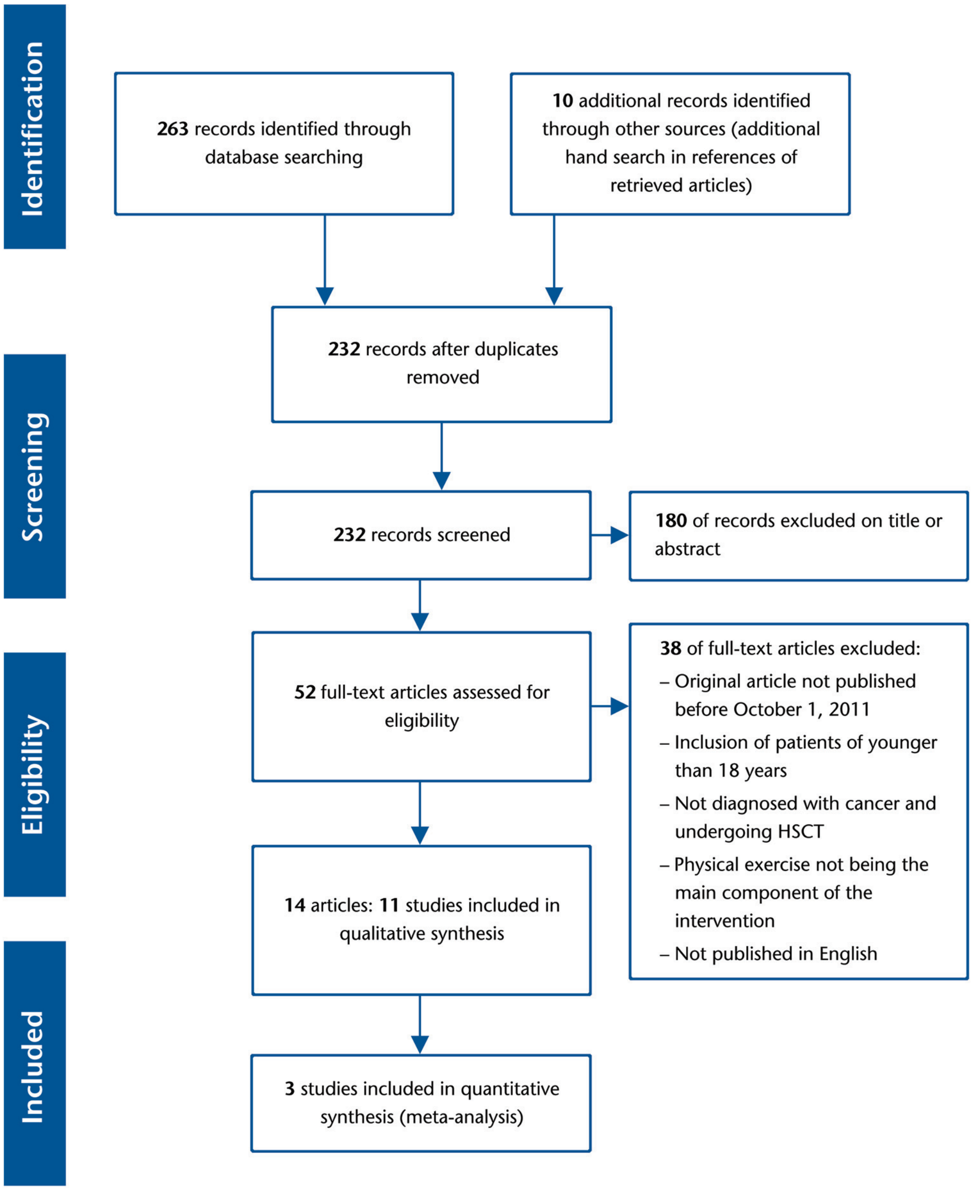

Figure 1.
PRISMA flow diagram of studies through the systematic review. HSCT=hematopoietic stem cell transplantation.

(I^2>75%).[20] A *P* value of ≤.05 indicated heterogeneity of treatment effects. A random-effects model was used to pool the effects of the studies, as we expected clinical heterogeneity among them.

Results

Figure 1 shows a flowchart of the selection process for literature search. After screening of titles and abstracts, 180 studies (78%) were excluded out of a total of 232 unique publications. The remaining 52 publications were read in full text. After reading the full article, 14 articles were included in this review.[21–34] Two author groups (Kim and Kim[21,22] and Jarden and colleagues[23,24]) each published 2 articles using the same study sample, but focusing on different outcomes. One author group published 2 articles where the second article included a subgroup analysis of their RCT.[25,26] Therefore, the actual total number of included original studies for this review was 11.

Assessment of Risk of Bias

The risk of bias of the RCTs is described in Table 1. The raters agreed on 58 of the 77 items being scored in the risk of bias assessments, resulting in a percentage agreement of 75%. Disagreement between the assessors was resolved

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by discussion, and in case of remaining discussion, a third assessor (I.vH.) was consulted for advice in order to make a final decision. After discussion and consulting, 100% agreement was reached.

The study by Knols et al[33] had the highest score (6 out of 7), corresponding to the lowest risk of bias. Overall, 4 studies attained a score of ≥4 out of 7 and had a low risk of bias. Overall scores of the other studies were less than 4 out of 7, corresponding to a high risk of bias. Methodological shortcomings regarding blinding of participants and personnel were present in all studies.[21–34] Lack of blinding of outcome assessments was present in all except 2 studies.[30,33] Other less prevalent shortcomings were lack of allocation concealment (8 studies),[21–24,27,29–32,34] lack of clarity regarding random sequence generation (6 studies),[27–31,34] incomplete outcome data (7 studies),[21,22,27,28,30,31,34] and lack of clarity regarding selective reporting (unclear in 2 studies).[21,22,34] Eight studies were considered free of other problems that could lead to a high risk of bias.[21–27,29,30,32,33] Three studies with low risk of bias could be pooled in our meta-analyses.[23,26,32] The other studies have been summarized and described.

Publication Bias

Funnel plots were performed for all outcomes, and all were symmetrically displayed (plots not shown).

Patient Characteristics

The studies were performed in several countries around the world: 5 in the United States,[27–31] 2 in Germany,[25,26,32] 1 in Denmark,[23,24] 1 in Korea,[21,22] 1 in Switzerland,[33] and 1 in Brazil.[34] Table 2 summarizes the important characteristics and significant results of all studies.

A total of 734 patients with different hematologic malignancies had been enrolled, with the number included ranging from 18 to 135. Of the 11 studies, 7 investigated patients receiving an allogeneic HSCT,[21–24,27,30,32,34] 2 looked at patients receiving an autologous HSCT,[28,29] and 3 involved patients receiving either an allogeneic or autologous HSCT.[25,31,33]

Two studies focused only on patients with multiple myeloma,[28,29] and 1 study included only patients with leukemia or severe aplastic anemia.[21,22] The remaining 8 studies investigated patients with any type of lymphoma or leukemia.[23–27,30–34]

Intervention

Four studies implemented the physical exercise intervention during hospital admission,[21–26] and the implemented exercises continued after hospitalization in 2 studies.[30,34] In 3 studies, the intervention programs started before hospitalization and continued during hospital admission as well as after discharge.[28,29,32] Three studies implemented the exercise intervention after discharge, with a follow-up period ranging from 3 weeks to 6 months after HSCT.[27,31,33]

Intervention programs differed markedly, with 5 studies using a combination of endurance training and resistance training.[27–29,32,33] One study investigated resistance exercise only[31]; another study investigated endurance training only[30]; a third study combined endurance training with dynamic exercises, progressive relaxation, and psychological education[23,24]; a fourth study combined endurance training with activities of daily living (ADL) training[25,26]; a fifth study examined a combination of endurance training, active range of motion, stretching exercises, and resistive training[34]; and the last study investigated a combination of bed exercises and relaxation breathing exercises.[21,22]

Endurance exercise programs mostly involved walking[27,28,30,32,34] (frequently on a treadmill) and cycling.[23–27,32,33] For the resistance exercises, stretch bands,[27–29,31,32] weight machines,[27] or free hand and ankle weights[23,24,27,33] were used.

The duration of the programs varied between 4 weeks[27] and approximately 6 months.[28] The control groups varied as well, with some controls receiving routine or usual care,[21–24,29–31,33] others offered no exercise program at all,[32,34] and others receiving so-called passive and active mobilization[25,26] or being instructed to exercise at home.[27,28] All studies evaluated the effect of the exercise program postintervention, although some studies also included an assessment during the exercise intervention.[28–30,32,34] Two studies also evaluated the effect of the intervention after follow-up periods of 3 and 6 months.[23,24,33]

QOL

Quality of life was assessed in 5 studies.[23,25,26,31–33] Three studies[23,26,32] had nearly comparable timing and content of intervention and were included in the meta-analysis for analyzing QOL (Fig. 2). These 3 studies included only patients receiving an allogeneic HSCT (n=148). Jarden et al[23] and Baumann et al[26] started their physical exercise intervention during hospitalization. Wiskemann et al[32] started their physical exercise intervention shortly before hospitalization and continued the intervention during the inpatient period and after hospitalization. The studies were only comparable and usable for a meta-analysis at the moment of discharge from the hospital. All 3 studies used the same QOL questionnaire, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), with an overall score ranging from 0 to 100 points and a higher score representing a

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Table 2.
Characteristics of All Studies Included in the Systematic Review[a]

Study	Study Participants	Moment, Duration, and Follow-up of Intervention	Intervention	Outcome Variables	Results[b]
Hacker et al, 2011[31]	Patients receiving allogeneic + autologous HSCT N=19 (9 IG, 10 CG)	When: supervised and nonsupervised strength training starting immediately after discharge from the hospital Duration: 6 wk Follow-up: postintervention (6 wk after discharge)	IG: strength training intervention, a comprehensive program of progressive resistance to strengthen the upper body, lower body, and abdominal muscles using elastic resistance bands Supervised: 1–2×/wk Nonsupervised: 1–2×/wk, a total of 3 times CG: recommendations regarding rest, physical activity, and exercise from their attending physician; participants were not told they could not exercise	Quality of life • EORTC QLQ-C30 • Quality of life (Ferrans and Powers QLI) Fatigue • Fatigue (1-item fatigue intensity scale and subscale of the EORTC QLQ-C30) Physical functioning • Muscle strength (timed stair climb, handgrip strength, 30-s chair stand test, time needed to stand up from bed rest examination) • Physical activity (Actiwatch [Philips Medical Systems Nederland BV, Best, Netherlands] score)	Fatigue • IG ↓ fatigue postintervention (P<.01)
Wiskemann et al, 2011[32]	Patients receiving allogeneic HSCT N=105, completed program n=80 (40 IG, 40 CG)	When: inpatient treatment (supervised) and outpatient treatment (nonsupervised, self-directed) before, during, and after HSCT, starting 1–4 wk before admission to the hospital until 6–8 wk after discharge from the hospital Duration: ±16 wk Follow-up: upon registration at hospital, discharge from hospital, 6–8 wk after discharge (postintervention)	IG: 3 endurance training sessions (up to 5 sessions during hospitalization) and 2 resistance training sessions per week CG: no exercise; participants were told that moderate physical activity is favorable during the treatment process, without further advice They were requested to wear a step counter and to record number of steps daily During hospitalization physical therapy was offered up to 3 sessions per week	Quality of life • EORTC QLQ-C30 Psychological well-being and distress • NCCN distress • HADS Fatigue • MFI • POMS Physical functioning • Isometric muscle strength (handheld dynamometer) • Functional performance status • Physical activity levels (pedometer step count) • 6MWT	Quality of life • EORTC physical functioning (P=.03) ↑ in IG postintervention Psychological well-being and distress • Global distress ↓ in IG at discharge from the hospital (P=.05) • HADS anxiety (P=.01) ↑ in IG postintervention Fatigue • IG less fatigue at 6–8 wk after discharge from the hospital in MFI general fatigue (P<.01) and physical fatigue (P=.01) + POMS fatigue (P<.01) • Group differences in MFI general fatigue (P=.03) and POMS fatigue (P=.01) at discharge from the hospital in favor of IG Physical functioning • Physical: IG ↑ in meters in 6MWT (P=.02) postintervention • Strength of lower extremities: ↑ for IG (P=.03) at discharge

(Continued)

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Table 2.
Continued

Study	Study Participants	Moment, Duration, and Follow-up of Intervention	Intervention	Outcome Variables	Results[b]
Baumann et al, 2011[26]	Patients receiving allogeneic HSCT N=47, completed program n=33 (17 IG, 16 CG)	When: inpatient treatment (supervised) starting −6 days after HSCT Duration: 7 wk Follow-up: postintervention at discharge	IG: supervised exercise therapy twice a day, including aerobic endurance training on a bicycle ergometer and ADL training CG: active and passive methods of mobilization with low intensities; individual treatment by a physical therapist for 20 min, 5 d/wk	Quality of life • EORTC QLQ-C30 Physical functioning • Patient endurance (endurance test according to the WHO scheme) • Strength (extensor muscles of the thighs) Other outcome measures • BMI • Lung function	Physical functioning • Relative endurance ↑ in IG and ↓ in CG (P<.01, group × time interaction) Other outcome measures • GVHD: ↑ in IG (P=.05)
Baumann et al, 2010[25]	Patients receiving allogeneic or autologous HSCT N=64 (autologous n=18/allogeneic n=46), completed program n=49 (24 IG, 25 CG)	See above	See above	Quality of life • EORTC QLQ-C30 Physical functioning • Patient endurance (endurance test according to the WHO scheme) • Strength (extensor muscles of the thighs) Other outcome measures • Hematopoietic parameters • Lung function	Physical functioning • Endurance performance was stable in IG and decreased in CG during course of hospitalization (P<.01, group × time interaction) • Endurance time was stable in IG and decreased in CG during course of hospitalization (P<.01, group × time interaction) • Relative endurance: ↑ in IG and ↓ in CG (P=.03, group × time interaction) • Strength: more ↓ in CG compared with IG (P<.01, group × time interaction)
Knols et al, 2011[33]	Patients receiving allogeneic or autologous HSCT N=131 (64 IG, 67 CG), completed program n=114, completed follow-up (3 mo) n=105	When: supervised treatment in patients from 3 wk to 6 mo after HSCT Duration: 12 wk Follow-up: postintervention and at 3 mo	IG: ambulatory physical exercise program, supervised for 12 wk; the program was performed twice weekly in a physical therapy practice or fitness center near the patient's home CG: usual care	Quality of life • EORTC QLQ-C30 • HRQOL (EORTC QLQ-C30, except for physical function) Fatigue • FACT-An Physical functioning • Knee extension • Grip strength (Jamar dynamometer [Sammons Preston Rolyan, Bolingbrook, Illinois]) • 15.2-m (50-ft) walk test • 6MWT • Quantified walking activity (Step Activity Monitor 3 [Cymatech Corporation, Seattle, Washington]) for 7 consecutive days) Other outcome measures • Body composition • IPAQ	Quality of Life • HRQOL: diarrhea ↓ (P=.01) in IG postintervention • HRQOL: emotional functioning ↑ (P=.02) in IG postintervention Physical functioning • IG ↑ knee extension strength (P=.001), ↑ walking speed (P=.007), and ↑ functional exercise capacity (P<.01) postintervention compared with CG over time • IG ↑ knee extension strength (P=.00) at 3-mo follow-up compared with CG over time

(Continued)

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Table 2.
Continued

Study	Study Participants	Moment, Duration, and Follow-up of Intervention	Intervention	Outcome Variables	Results[b]
Shelton et al, 2009[27]	Patients with lymphoma or leukemia receiving allogeneic HSCT N=61 (30 supervised, 31 self-directed), completed program n=53 (26 supervised, 27 self-directed)	When: supervised training group or patient-directed training group in patients less than 6 mo after HSCT Duration: 4 wk Follow-up: postintervention after discharge	IG: staff-supervised individualized exercise training program by a physical therapist consisting of aerobic and strengthening exercises, 3×/wk for 4 wk CG: self-directed home exercise training program; participants received instructions from a physical therapist assistant performing resistive exercises and a walking regimen at least 3×/wk	Fatigue • BFI Physical functioning • Strength of major muscle groups • ROM of upper- and lower-extremity joints • Lower-extremity sensation • Gait properties • PPT: 6MWT, 15.2-m (50-ft) fast walk test, unipedal stance time, forward reach, timed repeated sit-to-stand transfers	
Jarden et al, 2009[24]	Patients receiving allogeneic HSCT N=42 (21 IG, 21 CG), completed program n=34 (17 IG, 17 CG), completed follow-up (3 mo) n=30 (17 IG, 13 CG), completed follow-up (6 mo) n=29 (16 IG, 13 CG)	When: inpatient treatment (supervised) starting −7 days after HSCT Duration: 4–6 wk Follow-up: postintervention at discharge/3 mo/6 mo	IG: standard treatment and care and a 4- to 6-wk structured exercise program, progressive relaxation, and psychological education during hospitalization, 1 h/wk, 5 d/wk CG: usual care, including the department's standard of care of physical activity; physical therapy was offered following allogeneic HSCT (day +1), up to 1½ h weekly, varying from day to day and from patient to patient in mode, frequency, intensity, and duration	Physical functioning • KPS Other outcome measures • Longitudinal symptom cluster patterns in intensity scores • Prevalence, severity, and distress of self-perceived individual symptoms (SCT-SAS)	Other outcome measures • IG mean symptom severity scores, over time, ↓ compared with CG in 4 cluster groups (P=.02/P<.01/P <.01/P=.02)
Jarden et al, 2009[23]	See above	See above	See above	Quality of life • Quality of life (EORTC QLQ-C30) Psychological well-being and distress • HADS Fatigue • FACT-An Physical functioning • KPS • $\dot{V}O_2max$ • Muscle strength • Functional performance (2-min stair climb test) • Physical activity level Other outcome measures • Clinical outcomes	Other outcome measures • Parental nutrition ↓ days for IG (P=.02) Physical functioning • $\dot{V}O_2max$ ↑ for IG postintervention at discharge (P<.001) • Strength IG ↑ for chest press (P<.001), leg extension (P<.001), isometric right elbow flexors (P<.001), isometric right knee extensors (P<.001), and the stair test (P<.001) postintervention at discharge Other outcome measures • IG ↓ diarrhea, over time, compared with CG (P=.014)

(Continued)

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Table 2.
Continued

Study	Study Participants	Moment, Duration, and Follow-up of Intervention	Intervention	Outcome Variables	Results[b]
Coleman et al, 2008[29]	Patients with multiple myeloma receiving autologous HSCT N=135 (66 IG, 69 CG), completed program n=120 (short-term n=51, long-term n=69)	When: home-based individual exercise program during entire phase Duration: 3 mo Follow-up: prior to stem cell mobilization/following stem cell collection/before transplantation/after transplantation (postintervention)	IG: apoetin alfa (EPO) therapy (Total Therapy II) with a home-based individualized exercise program that incorporated aerobic and strength resistance training CG: EPO therapy (Total Therapy II) without home-based individualized exercise program, written exercise recommendations, advised to walk 20 min/d	Physical functioning • 6MWT + Borg Scale Other outcome measures • Number of attempts at and total number of days of stem cell collection • Number of RBC and platelet transfusions during the transplantation period • Time to recovery after transplantation • Response to intensive therapy for multiple myeloma	Other outcome measures • ↓ attempts for stem cell collection in IG (Bonferroni adjusted $P<.025$) • ↓ number of attempts at and total number of days of stem cell collection in IG (Bonferroni adjusted $P<.025$)
DeFor et al, 2007[30]	Patients receiving allogeneic HSCT N=100 (51 IG, 49 CG)	When: inpatient/home-based treatment (after HSCT) (supervised and nonsupervised) Duration: 100 d Follow-up: discharge from the hospital/postintervention	IG: inpatient period: walk for at least 15 min twice a day on a treadmill Home-based: walk once a day for at least 30 min CG: usual care, no treadmill unless requested by the patient or staff	Psychological well-being and distress • Self-perception of physical and emotional well-being Physical functioning • KPS Other outcome measures • Length of hospital stay • Survival	Psychological well-being and distress • Physical well-being ↑ in IG in total ($P<.01$) and ↑ in IG for patients receiving nonmyeloablative conditioning ($P<.01$) compared with CG at discharge • Emotional score ↑ in IG in patients receiving nonmyeloablative conditioning ($P=.02$) at discharge • Physical well-being ↑ in IG in patients receiving nonmyeloablative conditioning ($P<.01$) postintervention Physical functioning • KPS: patients receiving nonmyeloablative conditioning, less ↓ over time in IG ($P=.04$) compared with CG • KPS: more patients in IG who had baseline KPS <90 had KPS ≥90 by day 100 compared with CG ($P=.03$)
Kim and Kim, 2006[22]	Patients receiving allogeneic HSCT N=42 (21 IG, 21 CG), completed program n=35 (18 IG, 17 CG)	When: supervised exercise during the inpatient period Duration: 6 wk Follow-up: postintervention at discharge	IG: daily supervised bed exercises consisting of preliminary exercise, relaxation breathing, and finish exercise, a total of 30 min for 6 wk CG: routine care	Other outcome measures • T-cell subset percentages • CD3+, CD4+, and CD8+ % • CD4+/CD8+ ratio • Lymphocyte count	Other outcome measures • Lymphocyte count, group × time interaction ($P=.03$), ↓ in CG ($P<.05$) over time, ↑ in IG over time

(Continued)

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Table 2.
Continued

Study	Study Participants	Moment, Duration, and Follow-up of Intervention	Intervention	Outcome Variables	Results[b]
Kim and Kim, 2005[21]	See above	See above	See above	Fatigue • PFS	Fatigue • Pretest: affective meaning dimension ↑ in IG (P=.03) • The IG had more ↓ in fatigue in all dimensions compared with the CG (P=.01/P=.04/P=.001/P=.02)
Coleman et al, 2003[28]	Patients with multiple myeloma receiving autologous HSCT N=24 (14 IG, 10 CG), completed follow-up (3 mo) n=17, completed follow-up (6 mo) n=13 (attrition rate same for both groups)	When: individualized, home-based exercise program before, during, and after HSCT (nonsupervised) Duration: 6 mo, starting 3 mo before transplantation, ending 3 mo after first transplantation (24 wk) Follow-up: when first transplantation was received/ 3 mo after first transplantation	IG: exercise program combining strength with aerobic training for 20 min, 3×/wk CG: best practice usual care in terms of activity and rest provided by their physician, walk 20 min 3×/wk	Fatigue and psychological well-being and distress • POMS Physical functioning • Muscle strength • Aerobic capacity Other outcome measures • Sleep • Lean body weight	Other outcome measures • Average body weight per month: IG ↑, CG ↓ (P<.01)
Mello et al, 2003[34]	Patients receiving allogeneic HSCT N=32, concluded n=18 (9 IG, 9 CG)	When: inpatient and outpatient treatment during and after HSCT (supervised and nonsupervised) Duration: 6 wk Follow-up: after bone marrow engraftment (trial 2)/ postintervention after discharge (trial 3)	IG: an exercise program with active exercises, muscle stretching, and a walking-based program on a treadmill lasting 6 wk, daily on weekdays, during the inpatient period and continued when patient was at home CG: no exercise program	Physical functioning • Maximal isometric voluntary strength tests for the upper- and lower-limb muscle groups	Physical functioning • ↑ elbow flexors DM (P=.04) and hip abductors DM (P=.04) for the CG pre-BMT • In trial 3, IG ↑ hip flexors NDM (P=.01)

[a] IG=intervention group, CG=control group, MFI=Multidimensional Fatigue Inventory, POMS=Profile of Mood States, NCCN=National Comprehensive Cancer Network, HADS=Hospital Anxiety and Depression Scale, 6MWT=Six-Minute Walk Test, BMI=body mass index, IPAQ=International Physical Activity Questionnaire, FACT-An=Functional Assessment of Cancer Therapy–Anemia Scale, EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, WHO=World Health Organization, HCST=hematopoietic stem cell transplantation, ADL=activities of daily living, GVHD=graft versus host disease, $\dot{V}O_2$max=maximum oxygen consumption, DM=dominant, NDN=nondominant, HRQOL=health-related quality of life, ROM=range of motion, PPT=Physical Performance Test, BFI=Brief Fatigue Inventory, KPS=Karnofsky Performance Score, SCT-SAS=Stem Cell Transplantation Symptom Assessment Scale, PFS=Piper Fatigue Scale, RBC=red blood cell count, BMT=bone marrow transplantation.

[b] Only significant between-group differences (P<.05) are shown; ↑=significantly increased, ↓=significantly decreased.

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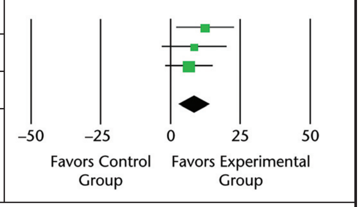
Study or Subgroup	Experimental Group			Control Group			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Baumann et al, 2011[26]	68.6	11.2	17	56.3	17.6	16	30.4%	12.30 (2.17, 22.43)
Jarden et al, 2009[23]	61.3	17.2	17	52.9	16.7	17	24.1%	8.40 (−3.00, 19.80)
Wiskemann et al, 2011[32]	53.8	19.9	40	47.3	18.1	41	45.5%	6.50 (−1.79, 14.79)
Total (95% CI)			74			74	100%	8.72 (3.13, 14.31)

Mean Difference IV, Random, 95% CI



Heterogeneity: $tau^2=0.00$; $\chi^2=0.76$, $df=2$ ($P=.68$), $I^2=0\%$
Test for overall effect: $z=3.06$ ($P=.002$)

Figure 2.
Forest plot of weighted mean difference (WMD), with 95% confidence interval (95% CI) for quality of life measured with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) at discharge from the hospital. IV=inverse variance.

higher QOL. For the moment of discharge from the hospital, the pooled analysis of the 3 studies revealed a significantly higher value for QOL in the allogeneic intervention group compared with the allogeneic control group (n=148; WMD=8.72; 95% CI=3.13, 14.31; P=.002). No heterogeneity for this outcome was found (I^2=0%, P=.68). Follow-up measurements were performed by Jarden et al[23] at 3 and 6 months postintervention, and they found no significant differences between groups for QOL. Wiskemann et al[32] continued the intervention program for 6 to 8 weeks after discharge from the hospital and found significant group differences in favor of the intervention group for EORTC "physical functioning" (P=.03) postintervention.

The studies of Hacker et al[31] and Knols et al[33] were not eligible for pooling in a meta-analysis. Although both studies started the intervention after discharge from the hospital, the programs differed in duration and starting point: duration of 6 weeks and starting following hospital discharge in the study by Hacker et al[31] and duration of 12 weeks and starting from 3 weeks to 6 months after HSCT in the study by Knols et al.[33] Hacker et al[31] found no significant effects between groups for QOL. Knols et al[33] found better scores for the intervention group on the health-related QOL outcomes of emotional functioning (P=.02) and diarrhea (P=.01) postintervention.

Psychological Well-Being and Distress

Four studies examined the effects of the exercise intervention on psychological well-being and distress.[23,28,30,32] One study had the exercise intervention during hospital admission,[23] a second study started during the intervention during inpatient period and continued it after discharge,[30] and 2 studies started the intervention before admission and continued it during admission and after discharge.[28,32] DeFor et al[30] used a self-perception scale of physical and emotional well-being, with scores ranging from 1 (very poor) to 10 (very good). Coleman et al[28] used the Profile of Mood States (POMS) with subscale scores for fatigue-inertia, tension-anxiety, depression-dejection, anger-hostility, vigor-activity, and confusion-bewilderment. Two studies used the Hospital Anxiety and Depression Scale (HADS) to measure general anxiety and depression,[23,32] whereas in the study of Coleman et al,[28] an overall score for mood disturbance was given based on the sum of the subscales. Pooling of results, therefore, was not possible. Although the study by DeFor et al[30] also gave a general single-point score for well-being, pooling of results with the study by Coleman et al[28] was not reliable because the POMS is a far more comprehensive questionnaire containing 65 items.

Jarden et al[23] and Wiskemann et al[32] both included aerobic and resistance/ADL training during their intervention. Because Wiskemann et al[32] continued the exercise program after hospitalization, the studies were only comparable and usable for the meta-analysis at the moment of discharge from the hospital. The results of the studies by Jarden et al[23] and Wiskemann et al[32] were pooled for the meta-analysis based on the HADS scores (eFigs. 1 and 2, available at ptjournal.apta.org). The HADS score ranges from 0 to 21 points, with a higher score indicating more severe anxiety and depression. When analyzing the anxiety score, no significant effects could be found at discharge from the hospital (n=115; WMD=−1.05; 95% CI=−3.67, 1.57; P=.43). Heterogeneity was found in this analysis (I^2= 80%, P=.03). When analyzing the depression score, no significant effects were found at discharge from the

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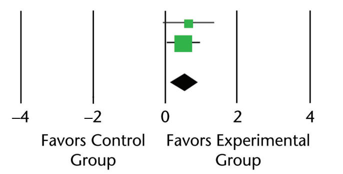
Study or Subgroup	Experimental Group			Control Group			Weight	SMD IV, Random, 95% CI	SMD IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Jarden et al, 2009[23]	33.9	9.7	17	27.8	9	17	29.1%	0.64 (−0.05, 1.33)	
Wiskemann et al, 2011[32]	−12.7	3.6	40	−14.7	4.4	41	70.9%	0.49 (0.05, 0.93)	
Total (95% CI)			57			58	100.0%	0.53 (0.16, 0.91)	

Heterogeneity: tau^2=0.00; χ^2=0.12, df=1 (P=.73), I^2=0%
Test for overall effect: z=2.81 (P=.005)

Figure 3.
Forest plot of standardized mean difference (SMD), with 95% confidence interval (95% CI) for fatigue at discharge from the hospital. IV=inverse variance.

hospital (n=115; WMD=−1.11; 95% CI=−2.37, 0.14; P=.08). Heterogeneity for this outcome was found to be moderate (I^2= 38%, P=.20). The study by Jarden et al[23] had follow-up measurements at 3 and 6 months postintervention. No significant effects were found for psychological well-being and distress at these follow-up moments. Wiskemann et al[32] continued the intervention program for 6 to 8 weeks after discharge from the hospital and found significant group differences, with a higher HADS anxiety score for the intervention group postintervention (P=.01). The meta-analysis showed no significant effect on psychological well-being and distress after hospitalization. This finding could be confirmed with the individual results of the study by Coleman et al,[28] where no significant effects also were found for psychological well-being and distress. In the study by DeFor et al[30] statistically significant effects in favor of the intervention group were found at discharge (P=.02/P<.01) and postintervention (P<.01).

Fatigue

Six studies examined the effects of the exercise intervention on fatigue.[21,23,27,31–33] Three of them started the intervention after discharge from the hospital.[27,31,33] These studies were not comparable in the meta-analysis because the intervention programs differed in duration (4, 6, and 12 weeks) and the moment of intervention (immediately after discharge from the hospital and up to 6 months after HSCT). Three studies implemented their intervention during admission to the hospital.[21,23,32] The study by Kim and Kim[21] assessed fatigue using the Piper Fatigue Scale (PFS). The PFS has no subscale for general fatigue and could not be used in the meta-analysis. Therefore, only the studies by Jarden et al[23] and Wiskemann et al[32] were included in the meta-analysis (Fig. 3).

Different questionnaires—the Functional Assessment of Cancer Therapy–Anemia Scale (FACT-An)[23] and the Multidimensional Fatigue Inventory (MFI)[32]—were used to assess fatigue, so the SMD was used as a summary statistic. There was a significant effect at discharge where the participants in the exercise group show less fatigue (n=115; SMD=0.53; 95% CI=0.16, 0.91; P=.005). No heterogeneity for this outcome was found (I^2=0%; P=.73). The meta-analysis indicated that training during hospitalization has a positive effect on fatigue in patients receiving an allogeneic HSCT. This effect could not be confirmed with the individual results of the studies by Shelton et al[27] and Knols et al[33] because no significant effects on fatigue were found between groups in these studies. Only Kim and Kim[21] and Hacker et al[31] found statistically significant effects for fatigue in favor of the exercise group.

Physical Functioning

Ten studies analyzed physical functioning, mostly the strength of muscles (n=8) and physical fitness (n=9).[23–34] The studies were not comparable for meta-analyses because treatment phase and duration differed. Moreover, outcome measures were not comparable because different muscle groups were assessed, noncomparable physical fitness measures were used, or subpopulations differed. Five studies showed significant effects in favor of the exercise groups after the intervention concerning strength,[23,25,32–34] with 4 studies having low risk of bias.[23,25,32,33] Physical activity and functional performance were presented in the studies to analyze physical fitness outcome measures for endurance.[23–33] Statistically significant effects in favor of the exercise group were found in studies with low risk of bias for maximum oxygen consumption,[23] Six-Minute Walk Test (6MWT) scores postintervention,[32] relative endurance over time,[25,26] walking speed over time,[33] and functional exercise capacity over time.[33] In studies with high risk

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of bias, statistically significant effects were found for the 6MWT,[27] 15.2-m (50-ft) walk,[27] body weight,[28] and Karnofsky Performance Score (KPS).[30] In the study by Jarden et al,[24] no significant effect for the KPS was found.

Other Outcome Measures

Significant effects in favor of the exercise group were found for requiring fewer attempts at stem cell collection (Bonferroni adjusted $P<.025$),[29] fewer days of stem cell collection (Bonferroni adjusted $P<.025$),[29] a better change in lymphocyte count,[22] fewer days of parental nutrition,[23] and a reduction in the incidence of diarrhea.[33] One study showed that more GVHD occurred in the intervention group.[26] The study by Jarden et al[24] showed that the exercise group had more declines in symptom severity scores over time. No significant effects were found in the study by Baumann et al[26] for lung function or hematopoietic parameters. In the studies by Baumann et al[26] and Knols et al,[33] no significant group effects were found for body composition.

Discussion

Eleven RCTs were identified, and exercise interventions differed in duration, type and content of exercise, and timing of the intervention relative to the HSCT. Moreover, different outcome measures were used. The results of our meta-analyses suggest that patients receiving an allogeneic HSCT may benefit from physical exercise, including improved QOL and reduced fatigue, especially at discharge from the hospital. Although no significant effects could be found in the meta-analyses for psychological well-being and distress, one study showed positive effects in the intervention group at discharge and at postintervention. Positive effects were found for the intervention group on physical outcomes concerning strength in 5 studies and for physical activity and performance in 8 studies. The other clinical outcome measures suggest exercise has a positive effect on recovery.

The risk of bias of the RCT studies included in this review appeared to be moderate to high, and no study was free of risk of bias. Moreover, the methodological quality score varied from 0[34] to 6 out of 7.[33] Lack of methodological rigor also was a limitation described in the previous reviews on this topic.[2,5,15] Methodological shortcomings regarding blinding of participants, personnel, and outcome assessment are hard to pursue in these kinds of intervention studies. To avoid potential bias, we included only RCTs in this review. In the previous 2 years, more RCTs of higher quality and using more valid and standard measurement methods have been published, which enabled us to pool data for meta-analyses. Therefore, the 3 studies pooled in our meta-analyses attained a score of higher than 4 out of 7 and had no high risk of bias.

The meta-analyses showed a significant positive effect at discharge from the hospital for QOL and fatigue, which is an important complaint during treatment for cancer.[9] Other studies also examined the effect of cancer on fatigue.[16,35,36] In the systematic review by Velthuis et al,[16] a supervised aerobic exercise program during breast cancer treatment appeared to be a promising and feasible approach in the management of fatigue. The study by Cramp and Daniel[36] also demonstrated that aerobic exercise is a potentially important intervention against fatigue. Our results from the meta-analyses support these findings for patients undergoing allogeneic HSCT, with the exercise group showing significantly less fatigue at discharge from the hospital than the control group. Other articles concerning exercise interventions in patients with cancer also showed these positive effects on QOL.[6,15,37,38] In previous reviews analyzing exercise interventions in patients undergoing HSCT, beneficial effects also were found for strength, endurance, physical fitness, fatigue, and psychological well-being.[2,5,15] It should be mentioned that the findings of these previous reviews must be interpreted with some caution. The previous reviews included studies with various study designs[2,5,15] and no restrictions regarding group size, age, and the use of a control group. In this review, the occurrence of GVHD was reported by one study to be higher in the exercise group.[26] The authors noted that more patients in the intervention group underwent unrelated allogeneic HSCT, which places them at higher risk of GVHD.

A potential limitation of our review might be the literature search. Due to our limitation in searching for RCTs published in English, it could be that a potentially relevant study in another language was missed. Another limitation was the pooling of studies in our meta-analyses. The pooling was limited due to the use of different intervention programs in the RCTs, with differences in admission, follow-up times, and outcome measures. For our meta-analyses, we included 3 studies.[23,25,32] Two of them were fully comparable in intervention duration.[23,25] Both interventions were conducted during the inpatient period and lasted approximately 6 weeks. The intervention in the third study[32] lasted longer, started shortly before hospitalization, and continued after hospitalization. Due to these differences in time and because different time moments for follow-up across studies further limited analyzing follow-up measurements, the studies were only comparable in our meta-analysis until the moment of discharge from the hospital.

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In this systematic review, the best results were seen in the meta-analyses at discharge from the hospital, suggesting that starting intervention before or just after transplantation seems to be effective. Starting intervention after hospitalization seems to be less effective, as fewer positive results were found in those studies. Looking at other patient groups, beneficial effects of physical exercise before surgery have been found for functional recovery with fewer complications afterward, suggesting that the earlier the intervention starts, the better.[39–41] In the review by Wiskemann and Huber,[5] tentative recommendations for moderate exercise, 30 minutes per session and 3 to 5 times per week, were given. Whether to start the exercise before, during, or after hospitalization is not made clear in the reviews by Liu et al,[2] Wiskemann and Huber,[5] and Knols et al.[15] With our review, we can suggest that it is beneficial to start a physical exercise program before or just after transplantation, as a positive trend is shown. It is not possible, however, to give clear advice for patients undergoing HSCT on either the best content of the exercise program or its start, duration, and intensity, as pooling of studies in our meta-analyses was limited. A clear clinical guideline concerning the start, duration, and intensity of the exercise program will require future RCTs that standardize these variables and use comparable outcome domains with similar outcome measures.

Nevertheless, the findings in this systematic review are of important clinical relevance because it is shown that the exercise interventions were well tolerated and safe for patients undergoing an HSCT. It appears that starting exercise intervention before or just after transplantation is beneficial because a positive trend is shown. This review indicates that physical exercise in aerobic or resistance training is feasible and beneficial in patients undergoing an HSCT. Exercise can be performed despite the frequent occurrence of medical complications. Further support for exercise as an adjuvant therapy for patients undergoing an HSCT is provided, but the optimal formula of the exercise program is still the subject of investigation.

All authors provided concept/idea/research design. Ms van Haren, Mr Timmerman, Dr Blijlevens, Dr Staal, and Dr Nijhuis-van der Sanden provided writing. Ms van Haren, Mr Timmerman, Dr Staal, and Dr Nijhuis-van der Sanden provided data collection and analysis. Ms van Haren, Mr Timmerman, and Dr Nijhuis-van der Sanden provided project management. Dr Blijlevens provided fund procurement. Dr Nijhuis-van der Sanden provided facilities/equipment. Dr Potting and Dr Blijlevens provided consultation (including review of manuscript before submission).

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